BEFORE THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

COMMENTS OF THE
AMERICAN CHEMISTRY COUNCIL
ETHYLENE OXIDE/ETHYLENE GLYCOLS PANEL

ON NTP CERHR'S DRAFT
EXPERT PANEL REPORTS ON ETHYLENE GLYCOL AND PROPYLENE GLYCOL

National Toxicology Program	)
Center for the Evaluation of Risks to Human Reproduction	)
Draft Expert Panel Reports on Ethylene Glycol and	)
Propylene Glycol; 67 Fed. Reg. 72965 (Dec. 9, 2002)	)

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EXECUTIVE SUMMARY

The Ethylene Oxide/Ethylene Glycols Panel (Panel) of the American Chemistry Council submits these comments in response to the December 9, 2002, *Federal Register* notice announcing the availability of the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction's (CERHR) draft Expert Panel report on ethylene glycol (Draft Report). The member companies of the Panel comprise the major domestic producers of ethylene glycol in the United States.

These comments provide the Panel's general and specific comments on the Draft Report. As discussed in these comments, there is a large body of developmental and reproductive toxicity, as well as metabolism and pharmacokinetic data on ethylene glycol. These data have been utilized to develop a PBPK model. When all these data and the PBPK model are considered together, it is clear that there is little likelihood of developmental or reproductive toxicity to humans from reasonably anticipated oral, dermal, or inhalation exposures that conceivably could result from the normal use of ethylene glycol or product containing ethylene glycol. Moreover, the available data strongly suggest that the potential for exposure by any route is very limited, and that exposure that might result from the normal use of product containing ethylene glycol is very low. The data described above indicate that any such exposures could not pose a risk of developmental or reproductive toxicity in humans.

The Panel believes that the Draft Report should also conclude that the NOAEL for developmental toxicity by oral gavage in mice is 500 mg/kg/day.

TABLE OF CONTENTS

INTRODUCTION

The American Chemistry Council Ethylene Oxide/Ethylene Glycols Panel (Panel) submits these comments in response to the December 9, 2002, *Federal Register* notice[1] announcing the availability of the draft Expert Panel Report on ethylene glycol and propylene glycol (Draft Report).[2] The member companies of the Panel comprise the major domestic producers of ethylene glycol in the United States.[3]

DISCUSSION

I. GENERAL COMMENT

The Draft Report should make an overall determination that ethylene glycol does not pose developmental toxicity or reproductive risks, taking into account the relevant toxicology data, the available metabolism and PBPK data and model, including those described in these comments, and reasonably anticipated exposures.

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1 67 Fed. Reg. 72965 (Dec. 9, 2002).

2 NTP CERHR, *NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Ethylene Glycol* (Dec. 2002) (Draft Report), available on the Internet at http://cerhr.niehs.nih.gov/news/EG-Report.PDF.

3 The ethylene glycol Panel members of the Ethylene Oxide/Ethylene Glycols Panel are: BASF Corporation, The Dow Chemical Company, Eastman Chemical Company, Equistar Chemicals, L.P., Huntsman Corporation, and Shell Chemical LP.

II. SPECIFIC COMMENTS

1.2.2 Use. (Page 2, Table 1-2): The Draft Report cites the Canada PSL2 *State of the Science Report for Ethylene Glycol* (Dec. 2000) (Health Canada Report) (9), as the source for the data summarized in Table 1-2. The data cited in support of the 3% concentration of ethylene glycol contained in household tub and tile cleaner do not support that percentage, or any percentage, of ethylene glycol in such products. The Health Canada Report uses the data reported by Flick (1986). The source of the information given in the Flick publication is Pilot Chemical Company. A review of the Material Safety Data Sheets (MSDSs) for all industrial cleaning products sold by Pilot, however, confirms that no product contains ethylene glycol. (Website review of all MSDSs.) In addition, the Panel recently received a letter from Pilot, included in Attachment 2, which states that Pilot does not make a tub and tile cleaner, but rather only manufactures and markets surfactant components that could be used in a tub and tile formulation.[4] Moreover, the 1996 edition of Flick does not indicate the presence of ethylene glycol in the household tub and tile cleaners listed. For these reasons, the concentration levels of ethylene glycol in tub and tile cleaner should be removed from Table 1-2. In addition, Flick (1996) does not indicate the presence of ethylene glycol in the windshield washer fluid, automotive wax and polish, and household floor wax and polish products identified in that reference. Flick (1986) was referenced for the percentages of ethylene glycol in Table 1-2 for those products.[5] Accordingly, the presence of any ethylene glycol, and therefore the percent of

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[4] Letter from Robert P. Cellura, Pilot Chemical Company, to Dr. William M. Snellings, November 28, 2001.

[5] *See* Health Canada Report at 20. Flick (1989) was also referenced for windshield washer fluid.

ethylene glycol identified in Table 1-2 for those products, is not substantiated by the much more recent edition of Flick, which would be more representative of current formulations than the editions of Flick in the 1980's. Further, the only windshield washer formulation listed in Flick (1989) as containing ethylene glycol was reported to be manufactured by Dow Chemical U.S.A. Dow has indicated that it has no information that the relevant divisions of Dow ever produced or sold a windshield washer fluid product containing ethylene glycol.[6] Therefore, any reference to ethylene glycol in those products should also be deleted. Moreover, the studies and/or sources referenced for other products listed in Table 1-2 are also old -- 1979 for ophthalmic solution and 1986 for cement sealer[7] -- and therefore also may not reflect current product formulations and contents.[8] Further, the lower limit (2.3%) indicated for latex paint is based on an evaluation of latex paints used in the United States (range from 2.3% to 2.6%), whereas the upper limit of 5% is based on an evaluation of paints manufactured in Canada.[9] The Draft Report should be revised accordingly.

1.2.3 Occurrence. The Panel recommends that the following corrections and clarifications to this section be made:

- The Draft Report (page 3) cites 1999 Toxics Release Inventory (TRI) data, stating that 8.8 million pounds of ethylene glycol were released to the atmosphere from U.S. manufacturing and processing facilities. The 2000

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6 Personal communication from David Gessford, Dow Chemical Company (Jan. 21, 2003).

7 Health Canada Report at 20.

8 The Panel has found no evidence that ethylene glycol is currently present in any ophthalmic solution products.

9 Health Canada Report at 20.

TRI data are available and should be cited. The 2000 TRI database indicates that the total release to the atmosphere was 4.6 million pounds, and the total environmental release was 7.1 million pounds.

- The Draft Report on the same page states that it has been estimated that 58 million pounds of ethylene glycol per year are released at the 17 busiest airports in the U.S. The document cited in support of this number (11) is a 1998 *Federal Register* notice publishing an Emergency Planning and Community Right-to-Know Act (EPCRA) Section 313 petition filed by certain organizations which in turn cites a 1994 report. As reported in the recent EPA document, *Preliminary Data Summary: Airport Deicing Operations (Revised),*[10] EPA has found "[i]ncreased use of anti-icing fluids as a means of reducing the volumes of deicing fluid needed," as one of the "trends among U.S. airports."[11] Moreover, the Preliminary Data Summary states: "Based on the limited quantitative data available to EPA, potassium acetate is now predominantly used for pavement deicing/anti-icing in the U.S. This is a change that has occurred over the past two to three years."[12] Further, airports have made significant improvements over the past several years in the use of a variety of methods to reduce the discharge of deicing fluids into the environment.[13]

- The Draft Report (page 3) states that Health Canada (9) cited "studies" reporting that approximately 0.87 g of ethylene glycol is released into the environment for every liter of antifreeze solution used in automobiles and that approximately 39% of all consumed antifreeze is lost to storm sewers.

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10 EPA, *Preliminary Data Summary: Airport Deicing Operations (Revised)* (Aug. 2000), available on the Internet at http://www.epa.gov/ost/guide/airport/airport.pdf (Preliminary Data Summary).

11 *Id*. at 1-3; *see also id*. at 6-4 ("[t]he principal advantage of [preventive anti-icing] is an overall reduction in the volume of glycol-based fluids applied to aircraft").

12 *Id*. at 12-6.

13 *See, e.g., id*. at 1-3 and 10-17. For example, the Preliminary Data Summary explains that over the past several years, airports have made improvements in the collection and treatment of deicing fluids, such as by utilizing contained deicing areas, increased recycling, and newly built storm water retention basins. *Id*. at 1-3 to 1-4, 10-17. There has also been an increased use of collection and containment for treatment and discharge into Publicly Owned Treatment Works (POTWs). *Id*. at 1-4. Moreover, as discussed in greater detail in the comments below, the National Pollutant Discharge Elimination System (NPDES) permit program requires measures to control pollutant discharges from airports. *See id.* at 12-3.

The Health Canada Report indicates that this information came from only a single l994 report.[14] The 1994 study may contain outdated data.

- Table 1-3 (page 4): The levels measured or modeled for surface water at the Winnipeg airport should be presented more fairly and completely, based on the Health Canada Report, so as to indicate that levels ranged from 2 to 660 mg/L in 1996, below 10 mg/L in 1997, and from largely undetected (8% frequency of detection) to 83 mg/L in 1998.[15]

- The airport data for surface water levels for the Newfoundland airport should specify the median information provided in the Health Canada Report -- 5 mg/L in 1997/1998 and 12 mg/L in 1998/1999.[16]

- The outdoor modeled air levels provided in the Draft Report (page 4, Table 1-3), for an ethylene glycol manufacturing plant in Alberta, which come from Health Canada (9), are of questionable relevance to U.S. manufacturing facilities, and, as discussed immediately below, are derived from outdated data and a less accepted methodology. Further, the Draft Report does not identify what the levels are intended to represent. While the Panel urges the CERHR Expert Panel to delete these data from the Draft Report, to the extent these data are retained, the Draft Report should indicate that, as stated by the Health Canada Report, the reported levels are intended to represent predicted maximum 24-hour average ground level concentrations at the specified distances from the property boundary, and that the annual frequency of occurrence of those concentrations was expected to be low.[17] The ethylene glycol air emissions from the facility used for the exposure estimates were those reported in the 1996 National Pollutant Release Inventory (NPRI). The 1996 emissions were abnormally high. The NPRI emissions were much lower in following years. The 1999 emissions are approximately 40% of the 1996 emissions. Moreover, the Draft Report, if it cites any data at all, should cite more refined and accurate data from Sciences International, Inc. (Sciences, 2002), which has conducted a refined modeling study to estimate average

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14 Health Canada Report at 10.

15 *Id.* at 15.

16 *Id.* It should also be noted that in 1994 the Government of Canada established a guideline under Section 53 of the Canadian Environmental Protection Act that established a glycol discharge limit of 100 milligrams per liter which is applicable to all federally owned or operated airports. This indicates that the data used in Table 1-3 may be outdated due to changes in the regulatory environment and glycol collection techniques.

17 *Id.* at 14.

outdoor ambient air concentrations outside the operating area fence line. Maximum annual average and maximum 24-hour average concentrations of ethylene glycol were identified where there are current residential dwellings and at selected points along the property line where additional exposures could occur. The ISC PRIME dispersion model was used and is generally favored by Environment Canada. Sciences International developed a conservative modeling approach to estimate short-term (24-hour) and long-term (annual) average off-site concentrations of ethylene glycol at the facility. The maximum outdoor 24-hour average concentration results are conservative because the contributions from the intermittent sources have considered only the worst-case meteorological conditions. The maximum predicted concentrations at a residence and at the property boundary where long-term exposure may occur were determined by the model. The maximum outdoor annual average concentration at a maximum nearby dwelling or residence was modeled to be 9.49 g/m^3. The maximum 24-hour average concentration was determined to be about 134 g/m^3 for the most plausible worst case combination of intermittent events at both the maximum nearby dwelling/residence and at the company outer boundary.

- The temperature for the vapor pressure indicated for ethylene glycol is incorrectly stated as 20 degrees C on page 3. It should be corrected to read 0.092 mmHg at 25 degrees C, consistent with page 1 and the Hazardous Substance Data Base (HSDB).

The Panel also recommends the following revisions to the last paragraph of this section (page 4).

- It should be clarified that ethylene glycol is approved as an ingredient starting material that is reacted with other materials in the manufacture of polyethylene terephthalate (PET) as opposed to just an ingredient.

- The regulation, 21 C.F.R. Section 172.820, cited in reference 12 should be replaced with 21 C.F.R. Section 178.3750. Section 172.820 refers to the conditions for use of polyethylene glycol when used as a direct food additive, whereas Section 178.3750 refers to the conditions for use of polyethylene glycol as an indirect food additive -- *i.e.*, conditions for its use as a component of articles intended for use in contact with food (*e.g.*, food wraps). Section 178.3750 therefore is the regulation relevant to the presence of ethylene glycol in food contact articles. To our knowledge, there is no production of regenerated cellulose films (RCF) used as food wraps in this country that contain ethylene glycol.

- This paragraph should not refer to the data described in Section 1.2.4 regarding the presence of ethylene glycol in food packaged in RCF and PET as data from "food surveys" since the data came from migration studies under controlled conditions, rather than market basket surveys. Moreover, this paragraph should note that the study was conducted in the United Kingdom (UK) and that the RCFs used to determine ethylene glycol migration into the foods were experimental RCFs not necessarily representative of RCFs which subsequently have been chosen for use in the UK for commercial food packaging or that are used in the United States for that purpose. This paragraph should also note that some of the ethylene glycol concentrations measured in the study exceeded the European Union (EU) migration limit of up to 30 mg/kg in food as a result of migration from RCF.

- The changes recommended above for the first paragraph of page 4 are indicated in the existing text by the italicized language as follows:

> "Ethylene glycol can be found in food due to its approved uses as an indirect food additive. Polyethylene glycol, an ingredient of regenerated cellulose films (RCF) used as food wraps, can contain ethylene glycol *(or ethylene glycol and diethylene glycols)* at 0.2% by weight [2000 ppm] *if the mean molecular weight of the polyethylene glycol is 350 or higher, and at 0.5% if the mean molecular weight is below 350 (12). [21 C.F.R. Section 178.3750 SHOULD BE CITED IN (12)].* Ethylene glycol is also approved as an ingredient *starting material that is reacted with other materials in the manufacture of* polyethylene terephthalate (PET), the material used to manufacture soft drink bottles (13). *Studies described in Section 1.2.4 demonstrated the presence of ethylene glycol in food packaged in experimental RCFs and in PET. The study of migration of ethylene glycol from experimental RCFs was conducted in the UK. The experimental RCFs used in that study were not necessarily representative of RCFs which subsequently have been chosen for use in the UK for commercial food packaging or of RCFs that are used in the United States for that purpose. In addition, some of the measured concentrations exceeded the migration limit of up to 30 mg of ethylene glycol per kg of food established by the current EU food contact directives. RCF directive (Directive 93/10/EEC, 1993 O.J. (L.93) 27 (limit applicable to food without physically free water at the surface); see also Directive 2002/72/EC (30 mg/kg limit applicable where plastic materials and articles are intended to come into contact with foodstuffs).*

1.2.4 Human Exposure

1.2.4.1 General Population Exposure. The Panel recommends that this discussion (page 5) be revised to indicate that PET bottles may contain at most only small amounts of unreacted ethylene glycol. The suggested revisions are indicated by the italicized language in the following excerpt from this section of the Draft Report:

- "Consumer exposure to ethylene glycol through food ingestion is possible if the food is packaged in polyethylene terephthalate (PET) bottles, which may contain *small amounts of* unreacted ethylene glycol, or in regenerated cellulose films (RCFs), which may contain polyethylene glycol as a softening agent." (Page 5.)

The Draft Report should also take note that both the Health Canada Report and the Concise International Chemical Assessment Document for Ethylene Glycol (CICAD) state that it is assumed that the vast majority of foods consumed in Canada contain no ethylene glycol.[18]

The data concerning migration of ethylene glycol from various types of cellulose wraps to various food types in Table 1-4 (page 5) are from Castle, *et al*. (1988a), a UK study.[19] Those data should not be considered in evaluating reproductive risks from ethylene glycol in the United States for a number of reasons. First, the RCFs were experimental, and as stated in the Castle article, "they may not, therefore, necessarily represent the precise compositions which

[18] Health Canada Report at 67; *CICAD 45 -- Ethylene Glycol: Human Health Aspects* (2002) at 26.

[19] Health Canada at 19; Castle, *et al*. (1988a).

have subsequently been chosen for commercial food packaging." If the RCFs used in the study were not necessarily representative of films used for commercial food packaging in the UK, they cannot be considered representative of commercial food packaging materials in the United States. The data should not be used for the additional reason that the RCFs, as discussed above, resulted in concentrations of ethylene glycol in several instances that exceed EU ethylene glycol migration limits. Further, the foods tested appear to be of a type that would not be commonly consumed in the United States.

The reference to ethylene glycol in French breads preserved with ethylene oxide (page 5) is based on a 1970 French study, which is dated and which represented French practices. The Panel is unaware of any US use of EO for bread preservation. This reference should be deleted as irrelevant to an exposure assessment.[20]

While the data regarding potential exposures from all routes of exposure appear to be limited, the data do suggest that any potential exposures from consumer products are likely to be either non-existent, or at most, extremely low. In any event, as discussed below, the relevant toxicology data, the metabolism and PBPK data and model, including those described in these comments, and any reasonably anticipated exposures demonstrate that ethylene glycol does not pose any developmental toxicity or reproductive risks.

[20] *See* Health Canada Report at 19.

1.2.4.2 Occupational Exposure

The Panel believes that certain corrections and clarifications should be made, and that certain additional information should be included in the discussion of occupational exposure.

- Pages 6-7: The Panel suggests that the discussion of the Gerin, *et al*. study (19) be corrected. The summary of this study in Table 1-5, footnote "b," should specify a total of 16-22 urine samples/time period for basket operators, 5 for each time period for coordinators, 7-9 for truck drivers, and 5-6 for lead. The statement on page 6 about the levels of diethylene glycol found in some air and urine samples should state that the levels of diethylene glycol were found at 1/5, 1/12, and 1/15 of the level of ethylene glycol in three air samples and 1/10 and 1/3 of the level of ethylene glycol in two urine samples. The statement beginning: "A total of 16 urine samples" should be revised so that the rest of the sentence reads: "had ethylene glycol concentrations, measured as creatinine concentrations, that exceeded the threshold value." Given that only a single sample in Table 1-3 exceeds the American Conference of Governmental Industrial Hygienists (ACGIH) limit of 100 mg/m^3, the Panel suggests that the last sentence in the bolded language (page 6) be revised to read: "The study does demonstrate that deicing operations *may* result in ethylene glycol mist exposures greater than the ACGIH limit of 100 mg/m^3 in workers, *although only one measurement exceeded that limit."* (Added language noted in italics, deleted language not shown.) The Panel also suggests that a statement be added noting that since this study was conducted, improvements have been made in deicing operations to limit exposure, including the use of enclosed baskets (cabs) and enclosed-basket deicing trucks to de-ice aircraft in some locations.[21] It also should be noted that if there were any indication that the ACGIH limit, which is a very short-term limit based on the respiratory and ocular irritative properties of ethylene glycol, could be exceeded, then appropriate engineering or personal protection equipment measures would be used to reduce any such exposure below the ACGIH limit.

- Pages 7-8: The Panel recommends that the Draft Report discuss a number of questions about the Laitinen, *et al*. study with regard to clinical chemistry, the analytical methodology, and the findings of ethylene glycol in the control samples which make the findings of this study questionable at best. Urine samples were not stored on ice, as is typically the case in

[21] Preliminary Data Summary at 6-18.

biochemical research. The levels of ammonia seen in the samples are likely attributable to the improper sample storage. In addition, the method used for quantification of ethylene glycol in the urine is unpublished, and has not been validated in the peer-reviewed literature. Moreover, measurements of ethylene glycol were inexplicably reported in urine samples from both workers and control subjects that were below the detection limits for the cited procedure of measurement.[22]

- Page 8: The Panel suggests that the discussion of the Abdelghani, *et al*. study (14) be corrected or clarified in certain respects. The impression is given in the Draft Report that the time-weighted average (TWA) values were measured in the breathing zones of the workers or otherwise were personal values. The TWA values were measured by placing monitors 8 inches above the bridge level at the front, middle, and end of the bridge. In addition, the two ranges given for the 15-minute ceiling values are specified in the Draft Report as for aerosols and mists, respectively. The ranges were given for aerosols (less than 0.05 to 2.33 mg/m^3) and for *vapor* (less than 0.05 to 3.37 mg/m^3). Further, the description in the Draft Report seems to suggest that the measurements, at least for the TWA values, occurred during a 6-9 hour period of spraying. Air samples to determine the TWA values were taken at about 2-hour intervals for approximately 8 hours (6-9 hour range) *following* spraying. The sampling for TWA values did occur on two separate dates, but the discussion implies that only 16 samples were obtained for such sampling. A total of 16 worker exposure samples were taken in the personal monitoring to determine the ceiling values, but the sampling frequency was different for the TWAs, as described above. The Draft Report should also clarify that the worker ceiling values were based on two separate 15-minute sampling times for each of the workers. Finally, it should be noted that since the TWAs were not measured in worker breathing zones and were monitored only 8 inches above the bridge level, they likely would overestimate worker exposure levels.

- This section of the Draft Report (occupational exposure section) should again make the statement on page 3 of the Draft Report that ethylene glycol has a low vapor pressure. It should also note that its potential for irritation would preclude high exposures, as demonstrated by Wills, *et al*. (1974). In addition, the Draft Report should note that the ACGIH limit of 100 mg/m^3 is a ceiling based on respiratory and ocular irritative effects which is not to be exceeded at any time, and that if there were any indication that the ACGIH limit could be exceeded, then appropriate

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[22] These issues are discussed in greater detail in "CMA Ethylene Glycol Panel Discussion on the Study 'Exposure to glycols and their renal effects in motor servicing workers' by J. Laitinen, J. Liesivuori, and H. Savolainen" (Oct. 25, 1996), which is included in Attachment 2.

engineering or personal protection equipment measures should be used to reduce any such exposure below the ACGIH limit.

- Page 6: The Draft Report should incorporate more recent, and better substantiated data regarding what happens to ethylene glycol used to de-ice aircraft and should explain recent trends in the adoption of measures for reduction in the release of ethylene glycol into the environment, as described above.[23]

- The Draft Report should also note with respect to airport anti-icing/deicing operations (page 6) that the National Pollutant Discharge Elimination System, established under the federal Clean Water Act, prohibits discharges of pollutants to the waters of the U.S. without a permit. This includes anti-icer/deicer contaminated storm water runoff, which in turn includes storm water runoff, snow-melt runoff, and surface runoff and drainage.[24] NPDES permits set monitoring requirements and limits on contaminants in storm water runoff from municipalities and certain businesses. The Draft Report should specifically note that NPDES permits are required for airport deicing operations, that NPDES permit limits on glycol runoff were imposed on airports beginning in 1995, and that control of deicer runoff from airports has become one of the key components of airports' NPDES permits. Several permitting alternatives are available, but all permits require the development and implementation of a Storm Water Pollution Prevention Plan that specifies pollution prevention and best management practices (BMPs) to control pollutant discharges.[25] As a result of ongoing NPDES permit requirements and, in some cases, effluent limitations, airports have made significant improvements in controlling pollutants through the implementation of pollution prevention BMPs. NPDES permits for storm water discharges from airports also require sampling, monitoring of discharges (at least for airports that have more than a specified number of flight operations per year), and recordkeeping.[26] Further, a group NPDES permit for storm water discharges regulating a substantial number of airports does not authorize dry weather discharges of anti-icing/deicing agents.[27]

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23 Preliminary Data Summary at 1-3 to 1-4.

24 *Id.* at 13-2; *see also* 40 C.F.R. § 122.26(b)(13).

25 Preliminary Data Summary at 12-3.

26 *Id*. at 13-4 to 13-6.

27 *Id*. at 13-7.

- It would be more accurate for the Draft Report (page 8) to state that the ACGIH ceiling exposure of 100 mg/m^3 is recommended to "minimize the potential for respiratory and eye irritation,"[28] and the 2002 TLVs and BEIs booklet should be cited, along with the 2001 ACGIH documentation, rather than the 2000 edition of the booklet.

1.4 Summary of Human Exposure Data. Changes should be made to this section that conform to the recommended changes discussed above. In addition, the Panel proposes a minor clarifying change (page 8) to reflect the fact that ethylene glycol is approved as a starting material that is reacted with other materials in the manufacture of PET, as indicated by the italicized language in the following text from this section:

- "Ethylene glycol is approved as an indirect food additive. It is used to manufacture polyethylene glycol, an ingredient of regenerated cellulose film (RCF) used as food wraps (12). Ethylene glycol is also an approved *starting* material *that is reacted with other materials in a chemical reaction to form* polyethylene terephthalate (PET), the material used to manufacture soft drink bottles (13)." (Page 8.)

2.0 General Toxicology and Biological Effects

2.1 Toxicokinetics and Metabolism

2.1.1.1.2 Inhalation. Given that only a single sample exceeded the ACGIH limit of 100 mg/m^3 in the Gerin study, the Panel believes that the last sentence in the bolded language (page 6) overemphasizes that sample. Accordingly, the Panel recommends that the sentence be revised in the same manner as the revisions proposed above with regard to the Gerin study.

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[28] ACGIH Documentation for Ethylene Glycol (2001) at 1 and 7.

2.1.1.2.3. Inhalation. The explanation of the Expert Panel's calculation of "dose" for the vapor pressure (page 15) from the study by Marshall and Cheng (37) is correct, but the calculation of dose for the aerosol exposure incorrectly used 30 minutes exposure instead of the actual 17 minutes exposure. Use of the correct exposure time results in an aerosol "dose equivalent" of 4.1 mg/kg rather than 7.1 mg/kg.

2.1.3 Metabolism

2.1.3.1 Humans. The Panel agrees with the statement that based upon the single pediatric poisoning case described (40) (pages 17-18), it is impossible to determine if children are more or less resistant to ethylene glycol-induced renal failure or can more readily metabolize glycolic acid than adults. The Draft Report states (page 18) in the "Strengths/Weaknesses" discussion that the "human data, while limited, provide data potentially useful for physiologically-based toxicokinetic (PBTK) modeling of ethylene glycol metabolism and elimination in humans." The Panel agrees that the data, while limited by uncertainties associated with determination of actual doses, time elapsed prior to blood sampling and the potential impacts of therapeutic interventions (dialysis, inhibitors, gastric lavage, etc.), provide potential benefits in developing PBTK models. The American Chemistry Council EO/EG Panel has sponsored a project to do exactly that. This project developed a human PBTK model from several *in vitro* experiments on human tissues, rat *in vivo* studies, and a single, controlled human

in vivo exposure study (*see* Figure 1).[29] In most cases the human PBTK model resulted in a reasonable description of the kinetics of ethylene glycol and/or glycolic acid in human case reports.

With regard to the discussion (page 17-18) of one case in reference 40 -- the 2 year old girl -- the Draft Report emphasizes that her glycolate/ethylene glycol ratio remained below unity throughout the kinetic course, while in adults the reverse is true (as in the other case in reference 40). The Draft Report has used this limited data to suggest that children may metabolize ethylene glycol consistently differently from adults. While the Panel agrees that more data are needed in this area, the data in this patient can be explained in another way that is not at all related to age. This child was admitted within 30 minutes of ingestion. Hence, although she initially had "raised" glycolate levels, these levels were relatively low compared to those observed in most human cases of overdose because of the short time after exposure (explaining why the glycolate/ethylene glycol ratio in the 2 year old girl starts below 1). Also, within a short period of time, she was given therapeutic amounts of ethanol to inhibit glycolate formation, so no more glycolate accumulation would have been expected. Both factors readily explain why the glycolate/ethylene glycol ratio never gets above 1 in this patient. Thus, there is a reasonable explanation for the kinetics/metabolism in this child -- not at all related to age.

2.1.3.2 Animals. In the "Strengths/Weakness" discussion of the published study by Pottenger, *et al*. (33) (page 23), the Draft Report notes that the Pottenger

[29] All the figures referenced in this discussion are included in Attachment 1 appended to

study was the first to address the issue of pregnancy and ethylene glycol disposition and was important for that reason. The Draft Report notes several strengths of the study, but also states that there are certain weaknesses or limitations in the study. While the Draft Report's comments on, and interpretation of, the Pottenger, *et al*. study are largely reasonable, the reviewers incorrectly characterize as limitations certain matters or the absence of certain measures or parameters, which were not relevant to the purpose of the study. The purpose of the study was to determine the dose-related changes in ethylene glycol and glycolic acid kinetics and whether pregnancy affected the kinetics. The study was not designed to be a mass-balance study since Frantz, *et al*. had already published such studies nor was it designed to provide insight into human kinetics. Thus, these can hardly be considered limitations. The reviewers should also reconsider their other concerns regarding the Pottenger, *et al*. study. First, half-lives for elimination, *per se*, may not be a good indicator of saturable clearance processes. It depends upon how they are calculated and the type of study they are based upon. In the Pottenger, *et al*. study, the half-lives were determined for the "beta" or elimination phase. Elimination phase half-lives can be similar across dose by definition, as they are calculated from the terminal, first-order clearance phase of the elimination curves where the concentrations have decreased below levels causing saturation (zero-order) of clearance processes. As to the oxalic acid blood levels being consistently at or near detection limits regardless of dose, this is, again, expected based upon the poor solubility of oxalic acid in blood. In the Pottenger, *et al*. study and numerous other studies where oxalic acid is determined in blood, the levels generally range from 5-10 µg/g based upon the limits of solubility (not rates of formation). Thus, there is a lack of dose-response to blood levels and the data are not "questionable" but accurately reflect the physico-

these comments.

chemical properties of oxalic acid. Further, the Draft Report (page 24) should state that the combination of the Frantz and Pottenger data sets establish that developmental toxicity in rats (NOEL 500 mg/kg; LOEL 1000 mg/kg) from exposure to ethylene glycol occurs as a result of the saturation of the mechanism for glycolic acid removal.

In discussing Carney, *et al*. (42) (pages 25, 45), which studied the effect of dose rate on ethylene glycol and glycolic acid blood levels in rats, the Expert Panel mentioned that "because AUC was not determined in this study, it is not known if bioavailability varied between the two dosing methods." While the Expert Panel ultimately agreed with the overall conclusions of the study authors, some additional clarification and AUC calculations can be provided to address concerns about differences in bioavailability affecting the developmental toxicity response. In the dose-rate study, the same route of administration (SC) was used in all groups, with some rats receiving ethylene glycol as single daily bolus injections, while other groups were administered the same daily ethylene glycol dose at a constant rate via subcutaneous infusion pump. Ostensibly, the use of the same route of administration would tend to favor equivalent bioavailability. Furthermore, a companion study by Carney, *et al*. (*Toxicologist* 66:139, 2002) showed that the kinetics of oral gavage dosing and subcutaneous bolus dosing with ethylene glycol are virtually identical. Finally, the similarity in blood ethylene glycol concentrations across pregnancy in the dose-rate study suggests that repeated dosing does not appreciably alter ethylene glycol kinetics.

Although blood sampling limitations essentially precluded the generation of daily blood concentration time courses in the SC bolus injection groups of the Carney, *et al*. dose-rate

study, the aforementioned data make it reasonable to use the detailed pharmacokinetic values from the Pottenger, *et al*. study as a surrogate to calculate AUC for the SC bolus group in the dose-rate study. The Pottenger, *et al*. study indicated an AUC for blood ethylene glycol of 2,928 µg-h/g for the 1,000 mg/kg/day dose level. In the constant rate infusion group of the dose-rate study, the average blood ethylene glycol concentration was 140 µg/g. Multiplying this by 24 hours yields an estimate of 3,360 µg-h/g for a 24-hour AUC in the 1,000 mg/kg SC constant rate infusion group. These AUC estimates indicate that the bioavailability of ethylene glycol was very similar between the two dosing methods, and was not a confounding factor in the dose-rate study.

In addition to the specific comments on the Metabolism Sections of the Draft Report provided above, the Expert Panel reviewers should be aware that a PBPK model has been developed to describe the kinetics of ethylene glycol and glycolic acid in pregnant and non-pregnant rats and humans (Corley *et al*., 2000; Corley, 2000; Carney *et al*., 2002). These studies are appended to these comments in Attachment 2. This model was developed from *in vitro* studies on partition coefficients, plasma protein binding, and metabolism of ethylene glycol and glycolic acid in blood and tissues from rats and humans, and from *in vivo* studies with ethylene glycol and glycolic acid in rats and humans. A diagram of the PBPK model is shown in Figure 1 and a list of *in vivo* studies used to develop or validate the PBPK model is shown in Figure 2.

Based upon the *in vivo* data, there appear to be significant strain differences in the metabolism of ethylene glycol to glycolic acid and the further clearance (metabolism and renal elimination) of glycolic acid. For example, a simulation of the concentration of blood levels of

glycolic acid following a single oral dose of 500 mg/kg glycolic acid in three different strains of rats (each weighing 300 g) are shown in Figure 4 along with a human (70 kg) for comparison. While the terminal elimination phase half-lives for the different rat strains (and human) are similar, the clearances of glycolic acid (defined as the dose/AUC) are significantly different between the various rat strains. The clearances of glycolic acid appear to scale allometrically (*e.g.,* follow the relationship $Y=aX^b$) for male F344 rats, female Sprague-Dawley rats, and humans, but not for male Wistar rats, as shown in Figure 4.

Using the PBPK model, administered dose or exposure vs. internal dose simulations were conducted to compare rats and humans. In this case, both the peak maternal blood concentrations of glycolic acid (Cmax) and AUC for glycolic acid in blood were determined following bolus oral dosing with ethylene glycol (Figure 5) and for 6-hour inhalation exposures to ethylene glycol (Figure 6). As demonstrated in these simulations, only high bolus oral dosing of >500 mg/kg ethylene glycol are expected to result in Cmax's for glycolic acid in human maternal blood that reach the 2 mM threshold for rat developmental toxicity suggested by Carney, *et al*. (2000) and Corley, *et al*. (2002). There is no apparent way for inhalation exposures to reach such a level especially with the limited vapor pressure of ethylene glycol and the potential for irritation that would preclude high exposures. According to Wills, *et al*. (1974), humans have been shown to tolerate only 15-minute exposures to aerosols of ethylene glycol at concentrations of 188 mg/m^3, 2 minutes of exposure to 244 mg/m^3, or only 2 breaths at 308 mg/m^3. The ratios of the animal developmental toxicity threshold of 2 mM to the peak blood concentrations of glycolic acid predicted by the PBPK model for humans are 5,300, 31,000 and 909,000 for each of these exposure scenarios, respectively. Thus, only intentional, high dose oral exposures are likely to result in blood levels of glycolic acid in humans that approach or

exceed the threshold maternal blood concentrations for fetal effects in rats.

3.2 Experimental Animal Data (Developmental Toxicity)

3.2.1 Oral Exposure

3.2.1.1.1 Mouse (Prenatal Toxicity Studies). The Draft Report discusses two mouse developmental toxicity studies conducted by the gavage route of exposure. These mouse gavage studies were published with companion studies conducted in rats (Price *et al.*, 1985; Neeper-Bradley *et al.*, 1995). The Price, *et al.* study utilized high doses of ethylene glycol, such that a NOEL for developmental toxicity was not established. To determine NOELs for the gavage route, subsequent developmental toxicity studies in mice and rats were conducted by Union Carbide Corporation and later published in Neeper-Bradley, *et al*. It should be clarified that the Draft Report's discussion of the mouse NOEL study cites the original Union Carbide report (Tyl and Frank, 1989), rather than citing the published version (Neeper-Bradley *et al.*, 1995), as was done for the rat NOEL study.

In evaluating the Tyl and Frank (1989) study, the Draft Report states that "There were no significant increases in the incidence of individual or total external or visceral malformations. The incidence of total malformations in litters was significantly increased in the 500 mg/kg bw/day group, but no individual type of malformation was reported to be statistically significant at that dose level." The only other effect at 500 mg/kg/day was a significant increase

in extra (14th) rib, which was classified as a skeletal variation. Based on these findings, the Draft Report considered 500 mg/kg/day to be a LOEL, with the next lowest dose level (150 mg/kg/day) the NOEL.

It should be noted that the incidence of total malformations may be useful as a preliminary screening level parameter, but may not be particularly useful in a case such as ethylene glycol in which there are abundant data and a well characterized profile of fetal effects. The incidence of total malformations pools treatment-related effects with anomalies that may have a genetic etiology or otherwise might be unrelated to treatment. It is preferable to examine specific patterns of malformations to assess biological significance, rather than rely solely on statistical significance, to interpret such fetal anomaly data. The study authors did not include this parameter in the published version of the study (Neeper-Bradley *et al.*, 1995), which implies that they did not find this parameter particularly useful.

As for the increase in the incidence of extra 14th rib, a number of studies have shown that this can simply be due to stress, that the effect is reversible, and that mice are particularly prone to expressing this variation. In the absence of any other specific skeletal effects, this single variation most likely does not represent an adverse effect. Finally, the combined weight of evidence from the many developmental toxicity studies on ethylene glycol indicates that the most sensitive fetal effect is a decrease in fetal body weight, which did not occur at 500 mg/kg/day. For all those reasons, it is more scientifically appropriate to consider 500 mg/kg/day as the study NOAEL, rather than 150 mg/kg/day. The Panel wishes to bring to the attention of the Expert Panel that the Health Canada Report concluded that the Neeper-

Bradley mouse study established a NOAEL of 500 mg/kg/day.[30]

3.4 Summary

The developmental toxicology data and the metabolism and PBPK data and model discussed in these comments and in the Draft Report clearly indicate that only high oral bolus doses of ethylene glycol have the capability of causing developmental toxicity in experimental animals. Slow dermal absorption rates and the low vapor pressure and irritating effects of ethylene glycol on the respiratory tract preclude the possibility of any dermal or inhalation exposure that would be comparable to high oral bolus doses. Because of the respiratory irritation effects of ethylene glycol that have been shown in a human study, the exposures would be limited (because higher levels have been shown to be intolerable) such that the blood levels of the developmental toxicant would be approximately four to five orders of magnitude lower than the blood level in the rat that is a threshold for developmental toxicity. Further, there is no appropriate use of ethylene glycol or a product containing ethylene glycol that would result in oral exposures that would be comparable to high oral bolus doses. Accordingly, there is little likelihood of risk of developmental toxicity to humans from reasonably anticipated exposures that could result from the appropriate use of ethylene glycol or any product that might contain ethylene glycol.

It should also be noted that the Panel believes, for the reasons discussed above,

[30] Health Canada Report at 64.

that the Draft Report should discuss the Neeper-Bradley, *et al*. (1995) oral mouse developmental toxicity study, the published version of Tyl and Frank (1989), and conclude that the NOAEL for that study is 500 mg/kg/day.

4.0 Reproductive Toxicity Data

4.2 Experimental Animal Data. The Draft Report should provide a more detailed explanation, based on the considerations discussed immediately below, as to why the Ren, *et al*. paper (101) regarding estrogenicity of ethylene glycol as assessed in a vitellogenin mRNA assay, does not provide any valid evidence that ethylene glycol has estrogenic effects. The Expert Panel concludes in the Draft Report that the **"**study does not provide much insight on ethylene glycol other than to suggest it may have weak estrogenic effects in fish**.**" The Draft Report also notes that the "study is of limited utility due to incomplete reporting." Beyond the problems of incomplete reporting, as well as the extraordinarily high dose levels used (up 18.4 grams/kg body weight) and an irrelevant route of exposure (IP injection), there are additional problems with this study that render it less than even "suggestive" of a weak estrogenic effect in fish. In assays such as this that assess mRNA levels using "Northern blotting" techniques, it is standard practice to include a control probe, such as beta-actin, to control for variability in the amount of RNA loaded onto different lanes of the gel electrophoresis apparatus. Typically, the amount of signal for the specific mRNAs of interest (*i.e.*, the estrogen-responsive genes, vitellogenin, and ER) are normalized to the beta-actin loading control. In the Ren, *et al*. study, the signals for the beta-actin control were reported, but they were not used to normalize the values for the estrogen-responsive genes. Instead, only non-normalized data for vitellogenin and ER were reported. As

can been seen in Figure 2 of the Ren paper, the beta-actin signal varied more than 2-fold from lane to lane, and was greatly increased in the very dose levels in which a weak estrogenic response was claimed. Thus, this was likely a false positive that may have been due to variability in overall mRNA loading from lane to lane. This conclusion is further supported by the lack of a dose-response relationship for the vitellogenin or ER responses. Importantly, the conclusion in the study report of estrogenic activity subsequently was retracted by coauthor and research leader, Professor J. Lech.[31] Moreover, on June 14, 2001, the Commission to the Council and the European Parliament on the Implementation of the Community Strategy for Endocrine Disrupters released a report which classified ethylene glycol as a substance "deemed NOT to be [an endocrine disruptor], on the basis of the available information."[32]

Other factors also should be discussed or briefly noted which establish that, while ethylene glycol causes developmental effects at high doses in rats and mice, those developmental effects do not result from endocrine mechanisms. These include the following:

- The database on ethylene glycol is very robust, and includes numerous developmental and reproductive toxicity studies, in addition to numerous acute, subchronic, and pharmacokinetic studies in both non-pregnant and pregnant animals. No effects have been observed on weights and/or histology of male or female reproductive or accessory sex organs in subchronic,[33] reproduction,[34] or chronic studies.

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31 Lech, J. (1997).

32 "Communication from the Commission to the Council and the European Parliament on the Implementation of the Community Strategy for Endocrine Disrupters," at 44 (Table 5). *See* http://europa.eu.int/eur-lex/en/com/cnc/2001/com2001_0262en01.pdf.

33 *See* Robinson, *et al*. (1990).

34 *See, e.g.*, Lamb (1985); DePass, *et al*. (1986 -- repro and dominant lethal mutagenesis study); DePass, *et al*. (1986) (chronic and onco study).

- At high doses, ethylene glycol induces a very specific signature of axial skeleton anomalies which are not at all characteristic of estrogenic or other endocrine active compounds (including 17-ß estradiol, testosterone, diethylstilbestrol, and other potent hormones).

- Based on structure-activity relationships, neither ethylene glycol nor its metabolites would be expected to bind to hormonal receptors, and it has been demonstrated that ethylene glycol does not bind to the estrogen receptor.[35]

- Studies have indicated that skeletal anomalies and body weight reductions in fetuses from ethylene glycol exposure were reversible,[36] indicating no in utero imprinting or other endocrine-related in utero toxicity.

- Ethylene glycol metabolism is well characterized and it is known that high oral doses result in a shift in ethylene glycol metabolism, leading to increased levels of the toxic metabolite, glycolic acid.[37] At low doses, glycolic acid is rapidly metabolized to carbon dioxide, and thus, does not accumulate.

- Studies on the mechanism of developmental toxicity demonstrate that glycolic acid and metabolic acidosis are responsible for the observed effects.[38] Furthermore, it appears that blood glycolic acid concentrations must exceed approximately 2 mmol/L to cause developmental effects. Achievement of such blood levels is highly unlikely for typical environmental exposures.

4.4 Summary

For the same reasons given above with respect to developmental toxicity, there is minimal risk of reproductive toxicity to humans from any reasonably anticipated exposures that

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35 Van Miller, J.P. "Brief Commentary: Ethylene glycol (EG) -- estrogen receptor binding assay." Internal Union Carbide Corporation report (July 1997), included in Attachment 2.

36 Marr, *et al*. (1992).

37 Carney (1994).

38 Carney, *et al*. (1999).

could result from the normal use of ethylene glycol or any product that might contain ethylene glycol.

CONCLUSION

There is a large body of developmental and reproductive toxicity, as well as metabolism and pharmacokinetic data, on ethylene glycol. These data have been utilized to develop a PBPK model. When all these data and the PBPK model are considered together, it is clear that there is minimal risk of developmental or reproductive toxicity to humans from any reasonably anticipated oral, dermal, or inhalation exposures that conceivably could result from the normal use of ethylene glycol or any product that might contain ethylene glycol. Moreover, the available data strongly suggest that the potential for exposure by any route is very limited, and that any level of exposure that might result from the normal use of any product that might contain ethylene glycol is very low. The data described above indicate that any such normal use exposures could not pose any risk of developmental or reproductive toxicity in humans.

The Draft Report should also conclude that the NOAEL for developmental toxicity by oral gavage in mice is 500 mg/kg/day.

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